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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,177	02/05/2007	Alejandro Balazs	C1233.70001US01	4085

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,177	BALAZS ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 03/31/2010 have been fully considered. Claims 1-13 are pending. The amendment has been entered. Claim 13 is withdrawn. Claims 1-12 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims **4-5, 9-11** under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only--, and/or, --cannot depend from any other multiple dependent claim is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102/Necessitated by Amendment

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims **1-3, 5-8, 10, 12** are rejected under 35 U.S.C. 102(b) as being anticipated by **Ghannadan et al,** (Int Arch Allergy Immunol, 127: 299-307, 2002).

Ghannadan et al, disclose a) contacting a biological sample of HMC-1 cell line with the mAb for endothelial cell C protein (CD201) and b) separating cells that bind to the mAb by

FACS analysis thereby producing a substantially pure population of EPCR+ hemmatopoietic stem cells (abstract, p 300 2nd column under flow cytometry; p 302 Table 2 column 1-2, 7and p 303, 2nd column under phenotype of HMC-1 section).

Ghannadan teaches (a) contacting a biological sample of HMC-1 cells with an affinity to bind EPCR under condition appropriate for binding and (b) separating the cells that bind to the affinity agent from those that do not bind. Therefore, Ghannadan anticipates the method steps of **claims 1, 6.** Thus Ghannadan anticipates producing a substantially pure population of hematopoietic stem cells as in **claim 1** and obtaining a substantially pure population of EPCR+ cells as in **claim 6.** Thus, Ghannadan teaches a composition of hematopoietic stem cells consisting essentially of EPCR+ cells as in **claim 12.**

Ghannadan teaches the affinity agent is the mAb for endothelial cell C protein (CD201), thus Ghannadan anticipates **claims 2, 7.**

Ghannadan teaches the step of separating cells is performed by fluorescence activating cell sorting, thus Ghannadan anticipates **claims 3, 8.**

Ghannadan teaches identical method steps as in claim 1, thus Ghannadan anticipates a substantially pure population of hematopoietic stem cells isolated by the method of claim 1, thus Ghannadan anticipates **claim 5.**

Ghannadan teaches the human HMC-1, to perform the method steps of claim 6, thus Ghannadan anticipates **claim 10.**

Thus, Ghannadan et al, anticipate the instant invention.

Applicants noted the “HMC-1" cells was misspelled as “HNC-1” in the previous office action. The examiner acknowledges the inadvertent typographical error and corrected in the current office action.

Applicants argue the HMC-1 cell line is an immature mast cell line derived from a patient with mast cell leukaemia. The HMC- 1 cell line does not produce hematopoietic stem cells. It would not have been possible to obtain hematopoietic stems cells from the HMC-1 cell line. Ghannadan et al. examined the expression of CD antigens on human mast cells and basophils using monoclonal antibodies and found that the endothelial cell C protein antibody had a 26-46% reactivity with the mast cell line HMC-1. The HMC-1 cell line is described as having many characteristics of immature mast cells and being useful for the study of mast cells and their constituents. Mast cells are highly specialized cells found resident in tissues throughout the body and play a role in allergy and anaphylaxis. Hematopoietic stem cells are a rare population of bone marrow cells with the capacity to reconstitute the entire hematopoietic system. The mast cell line does not produce hematopoietic stem cells and, therefore it would not have been possible to obtain hematopoietic stem cells using HMC-1 and an endothelial cell C protein antibody; Ghannadan et al. does not disclose a method by which hematopoietic stem cells can be obtained or a method by which a substantially pure population of hematopoietic stem cells can be obtained.

These arguments are not persuasive because Ghannadan teaches identical method steps as instantly claimed and the source of the biological sample as instantly claimed is broad and is not limited to any source thus the HMC-1 as a source of a biological sample anticipates the claimed invention. In addition, the teachings of Ghannadan that the endothelial cell C protein antibody had a 26-46% reactivity with the mast cell line HMC-1 as applicants note anticipates a substantially pure population of hematopoietic stem cells EPCR+ as instantly claimed. Thus, since Ghannadan teaches the identical method steps and a biological sample HMC-1 cell line derived from a patient with mast leukemia as applicants note then Ghannadan

anticipates the production of a substantially pure population of hematopoietic stem EPCR+ cells.

Claim Rejections - 35 USC § 103/Necessitated by Amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, **4,** 5-8, **9,** 10, **11,** 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Ghannadan et al,** (Int Arch Allergy Immunol, 127: 299-307, 2002) in view of **Goodell et al,** (J Exp Med, 183: 1797-1806, 1996).

Ghannadan et al, disclose a) contacting a biological sample of HMC-1 cell line with the mAb for endothelial cell C protein (CD201) and b) separating cells that bind to the mAb by FACS analysis thereby producing a substantially pure population of EPCR+ hemmatopoietic stem cells (abstract, p 300 2nd column under flow cytometry; p 302 Table 2 column 1-2, 7and p 303, 2nd column under phenotype of HMC-1 section).

Ghannadan teaches (a) contacting a biological sample of HMC-1 cells with an affinity to bind EPCR under condition appropriate for binding and (b) separating the cells that bind to the affinity agent from those that do not bind. Therefore, Ghannadan anticipates the method steps of **claims 1, 6.** Thus Ghannadan anticipates producing a substantially pure population of hematopoietic stem cells as in **claim 1** and obtaining a substantially pure population of EPCR+ cells as in **claim 6.** Thus, Ghannadan teaches a composition of hematopoietic stem cells consisting essentially of EPCR+ cells as in **claim 12.**

Ghannadan teaches the affinity agent is the mAb for endothelial cell C protein (CD201), thus Ghannadan anticipates **claims 2, 7.**

Ghannadan teaches the step of separating cells is performed by fluorescence activating cell sorting, thus Ghannadan anticipates **claims 3, 8.**

Ghannadan teaches identical method steps as in claim 1, thus Ghannadan anticipates a substantially pure population of hematopoietic stem cells isolated by the method of claim 1, thus Ghannadan anticipates **claim 5.**

Ghannadan teaches the human HMC-1, to perform the method steps of claim 6, thus Ghannadan anticipates **claim 10.**

Ghannadan et al, differs from the present invention for not teaching the biological sample consisting of bone marrow and the EPCR+ cells are murine EPCR+ cells as in the amended claims **4, 9** and the claim **11** which depend from claim 9.

However, at the time of the instant invention **Goodell et al** teach the separation of side population (SD) cells which exhibit the highest dye-dye efflux activity and most enriched for hematopoietic reconstitution activity by magnetic bead separation and these cells were shown in competitive repopulation experiments to contain the vast majority of HSC activity from **murine bone marrow** and to be enriched at least 1,000-fold for in vivo reconstitution activity (abstract and under M&Ms p 1798). Goodell suggests the stem cell purification strategy by the side population strategy cab be extended to human adult bone marrow, human umbilical cord blood and porcine bone marrow with Hoechst 33342 and observe a staining pattern remarkably similar to that which observed with routine cells and stained SP cells from human bone marrow with respect to cell surface markers found on human progenitor cells and in vitro culture assays (p 1805).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Ghannadan et al, by utilizing the Hoechst 33342 dye exclusion technology of Goodell in order to obtain a pure enriched population of EPCR+ cells in a murine biological sample from bone marrow, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification in order to produce side population (SD) cells of EPCR+ cells which exhibit the highest dye-dye efflux activity and most enriched for hematopoietic reconstitution activity by magnetic bead separation as taught by Goodell et al.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Applicants argue the teachings and deficiencies of Ghannadan et al. have been discussed in response to the previous 102 rejection. Ghannadan et al. does not disclose a method by which a population of hematopoietic stem cells can be obtained. HMC-1 is an immature mast cell line and it would not have been possible to obtain any hematopoietic stem cells. It also would not have been possible (or obvious) to obtain substantially pure populations of hematopoietic stem cells. Goodell et al. does not cure the deficiencies of Ghannadan et al. Even if a skilled artisan had combined the teachings of Ghannadan et al. and Goodell et al., it would not have been possible to obtain hematopoietic stem cells, since they are not produced by the HMC-1 cell line.

These arguments are not persuasive regarding the Ghannadan for the same reasons as discussed above. Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Ghannadan et al, by utilizing the Hoechst 33342 dye exclusion technology of Goodell in order to obtain a pure enriched population of EPCR+ cells in a murine biological sample from bone marrow, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification in order to produce side population (SD) cells of EPCR+ cells which exhibit the highest dye-dye efflux activity and most enriched for hematopoietic reconstitution activity by magnetic bead separation as taught by Goodell et al.

Claims **1-3, 5-8, 10, 12** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Ghannadan et al,** (Int Arch Allergy Immunol, 127: 299-307, 2002) in view of **Miyazato et al, ((Blood, 98:422-427, 2001).**

The teachings of Ghannadan et al, apply here as indicted above.

Ghannadan et al, do not teach column chromatography for the production of EPCR+ cells.

However, at the time of the instant invention **Miyazato et al,** teaches that it is routine in he art to isolate hematopoietic cells by column chromatograph. Miyazato et al, teach the PB or BM aspirates and mononuclear cells (MNCs) were purified from the specimens by the Ficoll-Hypaque density gradient centrifugation, labeled with AC133 MicroBeads and subjected to chromatography on miniMACS magnetic cell separation columns volunteers (p 423 under materials and methods). Portions of the MNC and AC1331 cell preparations were stained with Wright-Giemsa solution, or analyzed with a FACScan flow cytometer for the expression of CD34, CD38, and AC133. The number of blasts purified from the BM of leukemia patients was more than 100 times that purified from the BM of healthy volunteers (p 423 under materials and methods).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): “Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) “Obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt

variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Ghannadan et al, by utilizing column chromatography in order to obtain enriched population of EPCR+ cells in a biological sample, as taught by Miyazato et al, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification in order to produce a population of EPCR+ cells since Miyazato et suggest the number of blasts purified from the BM of leukemia patients was more than 100 times that purified from the BM of healthy volunteers.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Applicants argue the teachings and deficiencies of Ghannadan et al. have been discussed in response to the previous § 102 rejection. Ghannadan et al. does not disclose a method by which a population of hematopoietic stem cells can be obtained. It would not have been possible to obtain hematopoietic stem cells or substantially pure populations of hematopoietic stem cells using the cell line HMC-1, which is an immature mast cell line. Miyazato et al. does not cure the deficiencies of Ghannadan et al.

These arguments are not persuasive regarding the teachings of Ghannadan for the same reasons as discussed above. Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Ghannadan et al, by utilizing column chromatography in order to obtain enriched population of EPCR+ cells in a biological sample, as taught by

Miyazato et al, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification in order to produce a population of EPCR+ cells since Miyazato et suggest the number of blasts purified from the BM of leukemia patients was more than 100 times that purified from the BM of healthy volunteers.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAGDALENE K. SGAGIAS whose telephone number is (571)272-3305. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval

(PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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